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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,076	08/23/2006	Wolfgang E. Berdel	20490.003	7498

28381 7590 03/03/2009

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	
MAIL DATE	**DELIVERY MODE**
03/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,076	BERDEL ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21,24,26-37,39 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,24,26-37,39 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/08, 2/26/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18, 22-23, 25, 38, and 40 have been cancelled. Claim 41 has been newly introduced.

Applicant's arguments filed 11/17/08 have been fully considered but they are not fully persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21, 24, 26-27, 29, 31-37, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 has been amended to recite said tissue factor or said fragment thereof comprises an amino acid sequence selected from the group consisting of a sequence having at least 95% homology to SEQ ID NO: 1, a sequence having at least 95% homology to SEQ ID NO: 2, a sequence having at least 95% homology to amino acid positions 11 - 218 of SEQ ID NO: 2, a sequence having at least 95% homology to amino acid positions 1 - 210 of SEQ ID NO: 2, and a sequence having at least 95% homology to amino acid positions 1 - 214 of SEQ ID NO: 2.

Page 11 of the specification discloses that the tissue factor TF can be that of SEQ ID NO: 1 or a sequence with a homology of at least 95% to SEQ ID NO: 1. The specification does not

disclose nor contemplate sequences having at least 95% homology to SEQ ID NO: 2 or 95% homology to the recited subsequences of SEQ ID NO: 2.

Claim 39 is directed to a method of treating a patient with neoplastic disease and recites particular neoplastic diseases: lung carcinomas, sarcomas, breast cancer, malignant melanomas, prostate cancers and other urogenital tumors, endocrine-active tumors, and fibrosarcoma.

Page 13 of the specification discloses treating the following neoplastic diseases with the fusion polypeptides: bronchial carcinomas and other tumors of the thorax and mediastinum, breast cancers and other gynecological tumors, colorectal carcinomas, pancreatic carcinomas and other tumors of the gastrointestinal tract, malignant melanomas and other skin tumors, tumors in the head and neck region, prostate carcinomas and other urogenital tumors, sarcomas, endocrine-active tumors, leukemias and Myelodysplastic Syndromes and Hodgkin lymphomas and non-Hodgkin lymphomas. The specification does not disclose nor contemplate treating all lung carcinomas and fibrosarcomas embraced by the claim.

Claim 41 recites that the pharmaceutical composition of claim 34 can be administered orally. Page 14 of the specification discloses by packaging in pharmaceutical vehicles, which prevent cleavage of the fusion polypeptides in the gastrointestinal tract, the fusion polypeptides or pharmaceutical compositions may also be administered orally. However, claim 41 is not limited to these types of pharmaceutical vehicles for oral administration. As such, this claim is broader than the original disclosure.

Claims 19-21, 24, 26-37, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the fusion polypeptides set forth below set

forth below, does not reasonably provide enablement for all fusion polypeptides, nucleic acids, vectors, cells, and methods of treatment embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 19-21, 24, and 26-28 are directed to fusion polypeptides. Claim 34 is directed to a pharmaceutical composition comprising a fusion polypeptide.

Claims 29-30 are directed to nucleic acids encoding fusion polypeptides.

Claim 31 is directed to a vector and claims 32-33 are directed to cells.

Claims 35-37 are directed to pharmaceutical compositions comprising a nucleic acids, vectors, and cells, respectively.

Claims 39 and 41 are directed to methods of treating a patient with neoplastic disease by administering a fusion polypeptide.

The specification discloses production of specific fusion proteins, including cyclic fusion proteins:

tTF-GRGDSP (SEQ ID NO: 3; Fig. 14; designated tTF-RGD)

tTF-GNGRAHA (SEQ ID NO: 4; Fig. 15; designated tTF-NGR)

tTF-GALNGRSHAG (SEQ ID NO: 5; Fig. 16)

tTF-GCNGRCG (SEQ ID NO: 6; Fig. 17; designated tTF-cycloNGR1)

tTF-GCNGRCVSGCAGRC (SEQ ID NO: 7; Fig. 18; designated tTF-cycloNGR2)

tTF-GCVLNGRMEC (SEQ ID NO: 8; Fig. 19; designated tTF-cycloNGR3)

SEQ ID NOS: 3-8 are recited in claim 28. These sequences are encoded by SEQ ID NOS: 10-15, respectively. SEQ ID NOS: 10-15 are recited in claim 29. SEQ ID NOS: 33-38 are recited in claims 26-27 and form the peptide part of SEQ ID NOS: 3-8.

Tumor selectivity is disclosed as being due to the specificity of the RGD sequence for $\alpha_v\beta_3$-integrin and of the NGR sequence for CD 13 (aminopeptidase N). These receptors are disclosed as being expressed selectively and specifically at high density on tumor endothelial cells.

The instant specification evaluates only the fusion polypeptide of SEQ ID NO: 3 for selectively binding to $\alpha_v\beta_3$-integrin on endothelial cells (see at least Figure 6A-B). Neither the fusion polypeptide of SEQ ID NO: 4 nor any other fusion polypeptide containing NGR was tested for binding to CD 13 on tumor vessel endothelial cells in the instant specification.

Kessler et al. (2008) is post-filing date art and establishes that SEQ ID NOS: 3-4 and 6-8 bind to immobilized $\alpha_v\beta_3$-integrin. SEQ ID NO: 3 includes peptide RGD. SEQ ID NOS: 4 and 6-8 include peptide NGR. SEQ ID NOS: 6-8 are directed to cyclic peptides fused to tissue factor and SEQ ID NOS: 3-4 are directed to linear peptides fused to tissue factor. Only the fusion with SEQ ID NO: 3 (corresponding to instant SEQ ID NO: 33) was evaluated for selectively binding to HUVEC cells. (See at least Table 1 and Figures 4 A-B.) Fusion proteins containing SEQ ID NOS: 3-4 were shown to reduce tumor growth rate when injected into mice with human adenocarcinoma of the breast tumors. (See at least Table 2 and Figure 5.) Although Kessler et al. discusses in vivo results with melanoma tumors, the reference does not identify the structure of tTF-NGF7 and tTF-NGF8. (See at least Figure 7.) As such, these melanoma results are not persuasive.

Bieker et al. (published on-line, Blood, January 2009) is post-filing date art and discloses that tTF-NGR (fusion protein including SEQ ID NO: 4) had an effect against A549, M21, and HT1080 tumors in mice and had some effect against liver lesions in cholangiocarcinoma, a breast metastasis of adenocarcinoma of lung, and mesothelioma in human cancer patients. The reference is silent as to effects on multiple myeloma, metastatic germ cell tumors, and adenocarcinoma of the lung in these patients. It does not speak to any other neoplastic disorders. This reference does not speak to other fusion polypeptides embraced by the claims.

Claim 19 requires that the peptide portion (part (a)) of the fusion polypeptide be capable of "selectively binding said fusion polypeptide to tumor vessel endothelial cells." While GRGDSP (SEQ ID NO: 33) has been shown to have this capability for SEQ ID NO: 3, no other peptide disclosed in the specification or embraced by the claims has been shown to have this capability. Note that Bieker et al. does not disclose data concerning binding to tumor vessel endothelial cells. Kessler et al. does not provide data beyond the specification concerning binding to tumor vessel endothelial cells. It is not considered to be so predictable that any 3 to 30 amino acid peptide comprising RGD or NGR would have this ability in the presence or absence of a linker having up to 15 amino acids. (See for example claims 20-21.) It is not considered to be so predictable that a cyclic peptide (see claim 24) would have this ability even if the linear peptide did. The results of SEQ ID NO: 3 cannot be extrapolated to other peptides disclosed in the specification as part of fusion polypeptides or other peptides embraced by the claims as the structures of these peptides are highly diverse. For example, the specification does not demonstrate that SEQ ID NOS: 4-8 have this capability. Only the fusion polypeptide of SEQ ID NO: 3 contains the RGD sequence disclosed as being specific for $\alpha_v\beta_3$-integrin. Even if one

of ordinary skill in the art could infer that the effects shown by Bieker et al. and Kessler et al. are due to binding of the fusion polypeptide to tumor vessel endothelial cells, results for amino acids 1-218 of tTF fused to SEQ ID NOS: 3-4 and 6-8 are not commensurate in scope with the claims. These results could not be extrapolated to all peptides of 3 to 30 amino acids (with or with linkers) and the tissue factor or fragment thereof embraced by the claims. Applicant is reminded that the claims as presently written require that the peptide of 3 to 30 amino acids selectively binds the fusion polypeptide to a tumor vessel endothelial cell and that the bound fusion polypeptide activates blood clotting.

Claim 39 is directed to treating particular neoplastic disorders. The specification discloses the ability of the fusion polypeptide of SEQ ID NO: 3 to inhibit human malignant melanoma, human fibrosarcoma, and human lung carcinoma tumors in mouse models. (See at least Figures 7-8 and 34.) Arap et al. (see at least page 377) teaches that RGD specifically targets melanoma, sarcoma, and carcinoma. Kessler et al. and Bieker et al. address particular cancers as set forth above. The specification does not provide any information concerning the remaining tumors embraced by the claims (e.g. prostate cancers, urogenital tumors, endocrine-active tumors). The specification and prior art of record do not make clear whether these neoplastic diseases would have been known to express $\alpha_v\beta_3$-integrin receptors selectively and specifically at high density on tumor endothelial cells. For those neoplastic disorders where this would not have been true, one of ordinary skill in the art would not have been able to extrapolate the results for the fusion polypeptide of SEQ ID NOS: 3-4 and 6-8.

With respect to claims 35-37, the specification discloses using nucleic acids, vectors, and host cells to produce the fusion polypeptide. There is no guidance in the specification for using

nucleic acids, vectors, or host cells in any therapeutic capacity such as gene therapy. The specification discloses and exemplifies administration of the fusion polypeptide. The specification does not tell how to use these pharmaceutical compositions. It is noted that the cell of claims 32 and 33 is not isolated and could be construed as embracing transgenic animals which are not disclosed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-21, 39, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 as amended further comprises a linker at the C-terminus of tissue factor. It is presumed (but not clear from the claim language) that this linker is between the tissue factor and peptide of 3 to 30 amino acids. In addition, this claim is confusing in its dependency on claim 19. As amended, claim 19 indicates that the peptide of 3 to 30 amino acids is coupled to the C-terminus of tissue factor. A fair reading of claim 19 would be that it is directly coupled with no intervening sequence. As such, claim 20 would be in conflict with claim 19 by requiring an intervening sequence and claim 21 would not appear to further limit the subject matter of claim 19.

Claim 39 is directed to a method of treating a patient with neoplastic disease by administering a pharmaceutical composition to a patient. The claim does not make clear what

the effect the treatment must have. For example, is generalized activation of blood clotting sufficient or does the method require tumor infarct to meet the limitation of "treating"?

Claim 41 is grammatically confusing in reciting "intravenously, subcutaneously, orally, and intraperitoneal administration." It appears that the claim should recite "intravenous, subcutaneous, oral, and intraperitoneal administration."

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa